PATENT

C-3320/1

APPLICATION FOR UNITED STATES LETTERS PATENT

for

ORAL FAST-MELT FORMULATION OF A CYCLOOXYGENASE-2 INHIBITOR

by

Trang T. Le, Tugrul T. Kararli, Mark J. Kontny, Srikonda V. Sastry, Janaki R. Nyshadham and Arthur J. Pagliero, Jr.

EXPRESS MAIL MAILING LABEL

NUMBER EL 877206325 US

DATE OF DEPOSIT August 17, 2001

I hereby certify that this Patent Application is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 C.F.R. §1.10 on the date indicated above and is addressed to:

Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231.

Signature Bernadette M. Harper

ORAL FAST-MELT FORMULATION OF A CYCLOOXYGENASE-2 INHIBITOR

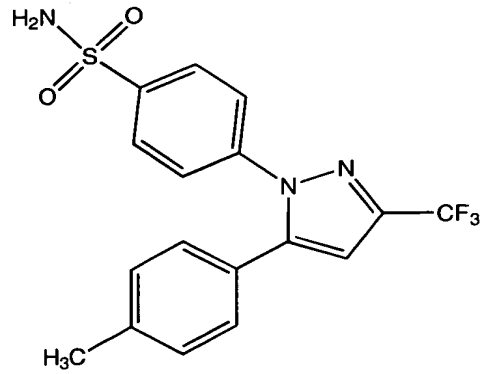
This application claims priority of U.S. provisional application Serial No. 60/226,349, filed on August 18, 2000.

FIELD OF THE INVENTION

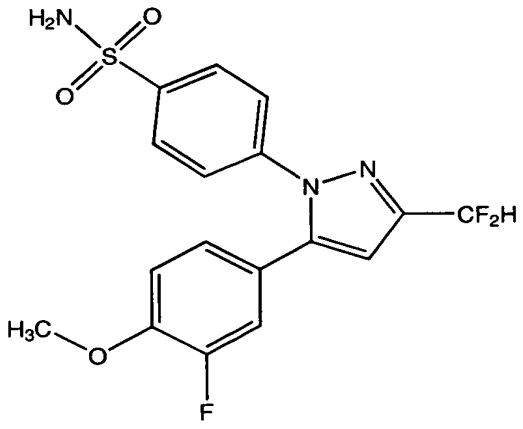
The present invention relates to orally deliverable pharmaceutical compositions containing a selective cyclooxygenase-2 inhibitory drug, to processes for preparing such compositions, to methods of treatment comprising orally administering such compositions to a subject in need thereof, and to the use of such compositions in the manufacture of medicaments.

BACKGROUND OF THE INVENTION

Numerous compounds have been reported having therapeutically and/or prophylactically useful selective cyclooxygenase-2 inhibitory effect, and have been disclosed as having utility in treatment or prevention of specific cyclooxygenase-2 mediated disorders or of such disorders in general. Among such compounds are a large number of substituted pyrazolyl benzenesulfonamides as reported in U.S. Patent No. 5,760,068 to Talley *et al.*, including for example the compound 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, also referred to herein as celecoxib (I), and the compound 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, also referred to herein as deracoxib (II).



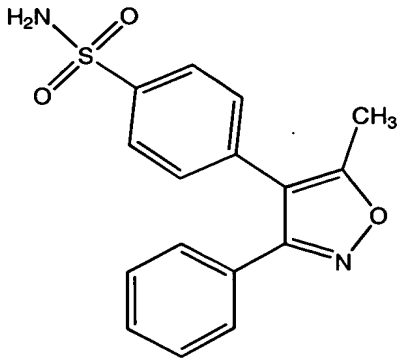
(I)



(II)

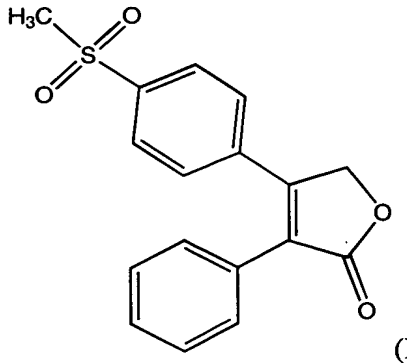
Other compounds reported to have therapeutically and/or prophylactically useful selective cyclooxygenase-2 inhibitory effect are substituted isoxazolyl benzenesulfonamides as reported in U.S. Patent No. 5,633,272 to Talley *et al.*,

including for example the compound 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide, also referred to herein as valdecoxib (III).



(III)

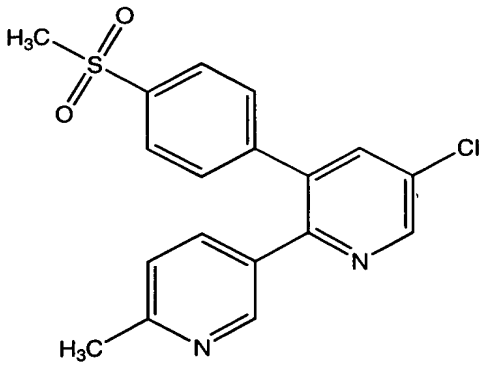
Still other compounds reported to have therapeutically and/or prophylactically useful selective cyclooxygenase-2 inhibitory effect are substituted (methylsulfonyl)phenyl furanones as reported in U.S. Patent No. 5,474,995 to Ducharme *et al.*, including for example the compound 3-phenyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one, also referred to herein as rofecoxib (IV).



(IV)

U.S. Patent No. 5,981,576 to Belley *et al.* discloses a further series of (methylsulfonyl)phenyl furanones said to be useful as selective cyclooxygenase-2 inhibitory drugs, including 3-(1-cyclopropylmethoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one and 3-(1-cyclopropylethoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one.

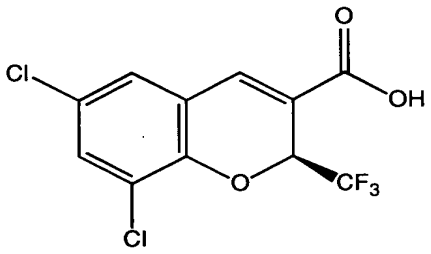
U.S. Patent No. 5,861,419 to Dube *et al.* discloses substituted pyridines said to be useful as selective cyclooxygenase-2 inhibitory drugs, including for example the compound 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine, also referred to herein as etoricoxib (V).



(V)

European Patent Application No. 0 863 134 discloses the compound 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one said to be useful as a selective cyclooxygenase-2 inhibitory drug.

U.S. Patent No. 6,034,256 to Carter *et al.* discloses a series of benzopyrans said to be useful as selective cyclooxygenase-2 inhibitory drugs, including the compound (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid (VI).



(VI)

International Patent Publication No. WO 00/24719 discloses substituted pyridazinones said to be useful as selective cyclooxygenase-2 inhibitory drugs, including the compound 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone.

A need for formulated compositions of selective cyclooxygenase-2 inhibitory drugs, in particular, easy-to-swallow compositions, exists. Easy-to-swallow drug delivery systems can provide many benefits over conventional dosage forms, particularly to populations such as the elderly, young children and other groups of patients that have difficulty swallowing conventional oral preparations.

Common oral dosage forms such as tablets, pills or capsules generally must be swallowed with water. Many pediatric and elderly patients with weak swallowing ability are unwilling or unable to swallow such dosage forms.

Powders and granules are additional commonly used oral dosage forms.

However, these formulations can be difficult to swallow completely due to their tendency to remain in the oral cavity. In some instances, patients taking powdered dosage forms will feel choked with powder or feel pain or unpleasantness due to granules being lodged under dentures. Additionally, powders and granules typically can only be used after the tearing or breaking of a package, tasks that elderly patients often find difficult to perform.

Further, powder and granule dosage forms are inconvenient to take as they typically must be diluted with a suitable amount of water or other liquid carrier prior to ingestion. This is particularly problematic when the medication is needed to provide fast relief of pain, since water is not always readily obtainable throughout the day. Moreover, powders or granules taken after dissolution or suspension in a liquid can also be difficult for elderly patients suffering from incontinence as such patients may experience urination problems at night when relatively large volumes of liquid-based medications are taken before bedtime.

Syrups and elixirs are additional commonly used oral dosage forms. However, elderly patients and others who have difficulty in measuring precise volumes are unlikely to be able to administer to themselves a proper dose and therefore require assistance at each administration.

International Patent Publication No. WO 00/32189, incorporated herein by reference, discloses various oral preparations of celecoxib. However, easy-to-swallow solid preparations of compositions containing selective cyclooxygenase-2 inhibitory drugs have not been disclosed.

In light of the expanding elderly population, it is becoming critically important to develop safe, effective, easy-to-swallow pharmaceutical preparations to treat age-related indications, wherein such preparations are convenient for elderly patients to self-administer and ingest.

U.S. Patent No. 5,576,014, incorporated herein by reference, discloses an intrabuccally dissolving compressed molding prepared by granulating together a low moldability saccharide with a high moldability saccharide and compressing the granulate into a molding. The resulting molding can incorporate a drug and is said to show quick disintegration and dissolution in the buccal cavity but to maintain sufficient hardness so as not break during production and distribution. The

compressed molding of U.S. Patent No. 5,576,014 is a type of dosage form known as a "fast-melt tablet", exhibiting rapid disintegration, usually associated with the carrier materials, typically sugars, and concomitant rapid dissolution or dispersion of the drug in the mouth, usually without need for water other than that contained in saliva. A drug formulated in such a tablet is readily swallowed.

However, selective cyclooxygenase-2 inhibitory drugs present certain challenges for formulation as fast-melt tablets. For example, many selective cyclooxygenase-2 inhibitory compounds, including celecoxib, deracoxib, valdecoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, etoricoxib and rofecoxib, have very low solubility in aqueous media. In addition, some, for example celecoxib, have relatively high dose requirements. Celecoxib also presents difficulties as a result of unique physical and chemical characteristics such as electrostatic and cohesive properties, low bulk density, low compressibility and poor flow properties.

Due at least in part to these properties, celecoxib crystals tend to segregate and agglomerate together during mixing, resulting in a non-uniformly blended composition containing undesirably large, insoluble aggregates of celecoxib. Therefore, it is difficult to prepare a fast-melt composition containing celecoxib that has the desired blend uniformity for rapid and complete disintegration in the mouth.

The term "fast-melt" as used herein refers to a composition such as a tablet wherein an active agent or drug is distributed or dispersed in a matrix formed by a carrier that, upon oral administration to a subject, disintegrates in the oral cavity, thereby releasing the drug, typically in particulate form, for entry to the gastrointestinal tract by swallowing, and subsequent absorption. The term "oral cavity" includes the entire interior of the mouth, including not only the buccal cavity (that part of the oral cavity anterior to the teeth and gums) but also the sublingual and supralingual spaces.

With respect to drugs requiring a high dose for therapeutic effectiveness, the large size of a fast-melt tablet required to provide a therapeutic dose may be a limiting factor. To reduce tablet size, drug loading can be increased in a given formulation. However, typical fast-melt tablet formulations begin to lose their rapid disintegration characteristics as the relative amount of active agent in the tablet increases, at least in

part because of the corresponding reduction in the amount of readily soluble and/or disintegratable carrier. Alternatively, several tablets having a low drug loading would have to be ingested, which can result in patient inconvenience and decreased compliance.

The physical and chemical characteristics of celecoxib described above also present challenges during granulation. In order to be compressed as tablets, drugs with poor flow and/or compressibility characteristics such as celecoxib must normally be granulated by a wet granulation method prior to tableting, for example by high-shear granulation or by fluid bed granulation.

The term "granulation fluid" as used herein refers to any liquid material that is added to a powder bed, for example by spraying, during fluid bed granulation or other wet granulation processes. The granulation fluid can, but is not required to, contain a binder and/or other excipients either in solution or in suspension. The term "powder bed" as used herein refers to all material including solid particulates and granulation fluid added thereto that is present in a granulation bowl at any point during wet granulation.

Fluid bed granulation provides several advantages over traditional high-shear wet granulation. For example, the handling required and the potential for contamination by dust are reduced. Fluid bed granulation also can be more readily automated than high-shear granulation and offers savings of both handling time and space. However, the above-mentioned challenges presented by celecoxib and other cyclooxygenase-2 inhibitory drugs of low water solubility can make fluid bed granulation difficult, particularly as drug loading increases. For example, celecoxib particles have an inherently electrostatic, cohesive nature that promotes agglomeration of the particles. Further, the highly water-insoluble, hydrophobic nature of celecoxib inhibits wetting of these agglomerated drug particles by the granulation fluid during granulation. This lack of wetting inhibits separation of the drug agglomerates. During the process of fluid bed granulation, such agglomeration and poor wetting can act to prevent complete fluidization of the material being granulated and ultimately lead to ineffective granulation.

Ineffective granulation can, among other effects, lead to formulation of non-uniform tablets which have low crushing strength and/or increased disintegration time,

characteristics which are highly undesirable for fast-melt tablets. Tablets with low crushing strength tend to break upon removal from blister packages or, alternatively, are too soft to maintain their individual integrity when bottled.

For these and other reasons, therefore, if some of the difficulties discussed above could be overcome, it would be a much desired advance in the art to provide a fast-melt formulation of a selective cyclooxygenase-2 inhibitory drug of low solubility, such as celecoxib, that can be produced by a conventional wet granulation process.

SUMMARY OF THE INVENTION

According to the present invention, there is now provided a process for preparing an oral fast-melt composition of a selective cyclooxygenase-2 inhibitory drug comprising (a) a step of wet granulating the selective cyclooxygenase-2 inhibitory drug together with a binding agent comprising a saccharide of high moldability, and (b) a step of blending with the drug a saccharide of low moldability, wherein the above steps (a) and (b) occur in any order or simultaneously to result in formation of granules. In a preferred embodiment, the process incorporates means to inhibit agglomeration of the drug.

The term "low moldability" as applied to a saccharide herein refers, in accordance with above-cited U.S. Patent No. 5,576,014, to a saccharide which generally shows a hardness of less than 2 kp when 150 mg of the saccharide is made into a tablet using a punch of 8 mm in diameter under a pressure of 10 to 50 kg/cm^2. Thus a saccharide of low moldability as required herein can be, for example, a "non-direct compression sugar" as defined in U.S. Patent No. 6,024,981 to Khankari *et al.*, the disclosure of which is incorporated herein by reference. In particular, a saccharide of low moldability typically has a fine particle size, for example an average particle size of about 10 μm to about 80 μm, and is not pre-granulated. Above-cited U.S. Patent No. 6,024,981 discloses that it is well known in the pharmaceutical industry that decreasing the particle size of a sugar decreases its compressibility and fluidity. Not all saccharides, even at fine particle size, are "non-direct compression sugars" or saccharides of low moldability as required herein. Examples of saccharides of low moldability, at least when in finely particulate form without pre-granulation, include lactose, mannitol, glucose, sucrose, xylitol, *etc.*

The term "high moldability" as applied to a saccharide herein refers, in accordance with above-cited U.S. Patent No. 5,576,014, to a saccharide which generally shows a hardness of 2 kp or more when 150 mg of the saccharide is made into a tablet using a punch of 8 mm in diameter under a pressure of 10 to 50 kg/cm^2. Thus a saccharide of high moldability as required herein can be, for example, a "direct compression sugar" as defined in above-cited U.S. Patent No. 6,024,981. Examples of saccharides of high moldability include maltose, maltitol, sorbitol, *etc.*

The means to inhibit agglomeration incorporated in a process of the invention is any measure taken during production of the fast-melt composition to prevent or reduce drug agglomeration or to facilitate separation of existing drug agglomerates. For example, in fluid bed granulation, means to inhibit agglomeration can include addition of a wetting agent, having the effect of providing improved wetting by the granulation fluid of the powder material to be granulated. Alternatively or in addition, means to inhibit agglomeration during granulation can include, for example, pre-wetting the powder material to be granulated, such as by employing an additional, external processor with spraying capacity, and/or using an air distributor plate adapted to increase air flow along the periphery of the granulation bowl. Other means for inhibiting agglomeration will be known to those of skill in the art and are encompassed herein.

Inhibition of agglomeration can be achieved by various mechanisms. The particular mechanism is not critical so long as the end result of reduced agglomeration and/or separation of agglomerates is achieved.

In a process of the invention, the selective cyclooxygenase-2 inhibitory drug, the saccharide of low moldability and, optionally, other excipients can, if desired, be separately wet granulated. However, in a presently preferred embodiment, a process of the invention comprises wet granulation of a selective cyclooxygenase-2 inhibitory drug together with a saccharide of low moldability and a saccharide of high moldability, more preferably also together with a wetting agent.

In another preferred embodiment, a process of the invention comprises a step of blending a selective cyclooxygenase-2 inhibitory drug with a saccharide of low moldability, followed by a step of wet granulating the resulting blend with a saccharide having high moldability and a wetting agent.

In still another preferred embodiment, a process of the invention comprises wet granulation of a saccharide having low moldability with a saccharide having high moldability to obtain granules of a first kind, wet granulation of a selective cyclooxygenase-2 inhibitory drug together with a saccharide having high moldability and a wetting agent to obtain granules of a second kind, and admixing the granules of said first and second kinds.

An especially preferred process of the invention further comprises a step of compressing the wet granulated, for example fluid bed granulated, composition prepared by any of the processes summarized above to produce a solid dosage form, for example an oral fast-melt tablet.

An oral fast-melt composition having a selective cyclooxygenase-2 inhibitory drug dispersed in a matrix comprising a saccharide of low moldability and a saccharide of high moldability, is a further embodiment of the present invention. A preferred composition of this embodiment is an oral fast-melt tablet. A still further embodiment is an oral fast-melt composition, for example, an oral fast-melt tablet, prepared by a process as herein described.

Preferred tablets of the invention disintegrate within about 30 to about 150 seconds after placement in a standard *in vitro* disintegration assay (*e.g.*, conducted according to U.S. Pharmacopeia 24 (2000), Test No. 701) and/or disintegrate within about 5 to about 60 seconds after placement in the oral cavity of a subject. Preferably, such tablets have a hardness of about 1 kp to about 10 kp.

In a particularly preferred embodiment of the invention, an oral fast-melt pharmaceutical composition is provided, comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility dispersed in a matrix comprising a saccharide of low moldability, a saccharide of high moldability and a wetting agent. Such a composition can be prepared by a process herein described or by any known process. The term "dispersed" in the present context means that the drug is substantially non-agglomerated. The wetting agent is present in an amount sufficient to inhibit agglomeration of the drug during preparation of the composition. Compositions of this embodiment are preferably tablets having disintegration and hardness properties as defined above.

Processes of the present invention have been found to resolve at least some of

the difficulties alluded to above in a surprisingly effective manner. Thus, in a significant advance in the art, a selective cyclooxygenase-2 inhibitory drug of low water solubility is now presented in a novel, easy-to-swallow, fast-melt formulation. A particular advantage of processes of the invention is that oral fast-melt tablets containing a cyclooxygenase-2 inhibitory drug of low water solubility, even such a drug having a relatively high dosage requirement, for example celecoxib, can be prepared by fluid bed granulation and compression. These oral fast-melt tablets provide a heretofore nonexistent dosage form of a selective cyclooxygenase-2 inhibitory drug that is efficient to produce, convenient and easy to swallow.

Also provided by the present invention are methods for therapeutic and/or prophylactic use of compositions of the present invention, and a method of use of a composition of the invention for preparing a medicament. Other features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE INVENTION

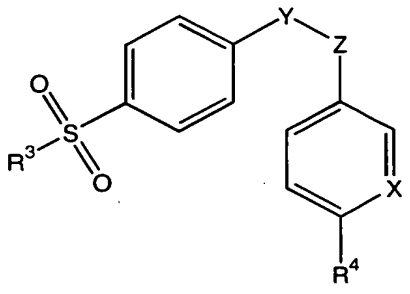
The present invention provides a process for preparing an intraorally disintegrating pharmaceutical composition, *i.e.*, an oral fast-melt composition, of a selective cyclooxygenase-2 inhibitory drug. The process comprises a step of wet granulating the drug together with a binding agent comprising a saccharide of high moldability, and a step of blending with the drug a saccharide of low moldability. The wet granulating step and the blending step can take place in any order or simultaneously to form granules. The process incorporates means to inhibit agglomeration of the drug. Compositions prepared by such a process represent an embodiment of the present invention.

A further embodiment of the invention is an intraorally disintegrating pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility dispersed in a matrix comprising a saccharide having low moldability, a saccharide having high moldability and, preferably, a wetting agent, the wetting agent being present in an amount sufficient to inhibit agglomeration of the drug during preparation of the composition.

A further embodiment of the invention is an intraorally disintegrating pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility dispersed in a matrix comprising a saccharide having low

moldability, a saccharide having high moldability, and a glidant, preferably silicon dioxide. Such a composition can further comprise a wetting agent.

Processes and compositions of the invention are especially useful for selective cyclooxygenase-2 inhibitory compounds having solubility in water lower than about 1 mg/ml. In particular, processes and compositions of the invention are suitable for compounds having the formula (VII):



(VII)

where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups. Preferred such five- to six-membered rings are cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

Illustratively, processes and compositions of the invention are suitable for celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone, more particularly celecoxib, valdecoxib, rofecoxib and etoricoxib, and still more particularly celecoxib and valdecoxib.

The invention is illustrated herein with particular reference to celecoxib, and it will be understood that any other selective cyclooxygenase-2 inhibitory compound of low solubility in water can, if desired, be substituted in whole or in part for celecoxib in processes and compositions herein described.

Preparation of a selective cyclooxygenase-2 inhibitory drug

Celecoxib used in the process and compositions of the present invention can

be prepared by a process known *per se*, for example by processes set forth in U.S. Patent No. 5,466,823 to Talley *et al.* or in U.S. Patent No. 5,892,053 to Zhi & Newaz, both incorporated herein by reference. Other selective cyclooxygenase-2 inhibitory drugs can be prepared by processes known *per se*, including processes set forth in patent publications disclosing such drugs; for example in the case of valdecoxib in above-cited U.S. Patent No. 5,633,272, and in the case of rofecoxib in above-cited U.S. Patent No. 5,474,995.

Dosage provided by compositions of the invention

Celecoxib compositions of the present invention preferably comprise celecoxib in a daily dosage amount of about 10 mg to about 1000 mg, more preferably about 25 mg to about 400 mg, and most preferably about 50 mg to about 200 mg.

For other selective cyclooxygenase-2 inhibitory drugs, a daily dosage amount can be in a range known to be therapeutically effective for such drugs. Preferably, the daily dosage amount is in a range providing therapeutic equivalence to celecoxib in the daily dosage ranges indicated immediately above.

Dosage units of celecoxib compositions of the invention typically contain about 10 mg to about 400 mg of celecoxib, for example, a 10, 20, 37.5, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 or 400 mg dose of celecoxib. Preferred dosage units contain about 25 mg to about 400 mg of celecoxib. More preferred dosage unit forms contain about 50 mg to about 200 mg of celecoxib. A particular dosage unit can be selected to accommodate the desired frequency of administration used to achieve a specified daily dosage. The amount of the unit dosage form of the composition that is administered and the dosage regimen for treating the condition or disorder will depend on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the condition or disorder, the route and frequency of administration, and the particular selective cyclooxygenase-2 inhibitory drug selected, and thus may vary widely. It is contemplated, however, that for most purposes a once-a-day or twice-a-day administration regimen provides the desired therapeutic efficacy.

In a celecoxib composition, celecoxib can be present in the composition at a minimum concentration of about 1%, preferably about 4%, more preferably about 10%, and still more preferably about 20%, by weight. Where the selective

cyclooxygenase-2 inhibitory drug is therapeutically effective at lower dosages than celecoxib, the minimum concentration can be lower than that indicated immediately above for celecoxib; for example in the case of valdecoxib the drug can be present at a minimum concentration of about 0.1% by weight. Celecoxib can be present in the composition at a maximum concentration of about 60%, more typically about 50%, by weight.

Utility of compositions of the invention

Compositions of the present invention are useful in treatment and prevention of a very wide range of disorders mediated by cyclooxygenase-2 (COX-2), including but not restricted to disorders characterized by inflammation, pain and/or fever. Such compositions are especially useful as anti-inflammatory agents, such as in treatment of arthritis, with the additional benefit of having significantly less harmful side effects than compositions of conventional nonsteroidal anti-inflammatory drugs (NSAIDs) that lack selectivity for COX-2 over COX-1. In particular, such compositions have reduced potential for gastrointestinal toxicity and gastrointestinal irritation including upper gastrointestinal ulceration and bleeding, reduced potential for renal side effects such as reduction in renal function leading to fluid retention and exacerbation of hypertension, reduced effect on bleeding times including inhibition of platelet function, and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects, by comparison with compositions of conventional NSAIDs. Thus compositions of the invention comprising a selective COX-2 inhibitory drug are particularly useful as an alternative to conventional NSAIDs where such NSAIDs are contraindicated, for example in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; gastrointestinal bleeding, coagulation disorders including anemia such as hypoprothrombinemia, hemophilia or other bleeding problems; kidney disease; or in patients prior to surgery or patients taking anticoagulants.

Such compositions are useful to treat arthritic disorders, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.

Such compositions are also useful in treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendinitis, bursitis, allergic neuritis, cytomegalovirus

infectivity, apoptosis including HIV-induced apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, burns, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following ophthalmic surgery such as cataract surgery or refractive surgery.

Such compositions are useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis.

Such compositions are useful in treating inflammation in such diseases as migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like.

Such compositions are useful in treatment of ophthalmic diseases, such as retinitis, scleritis, episcleritis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to eye tissue.

Such compositions are useful in treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis, and in bone resorption such as that associated with osteoporosis.

Such compositions are useful for treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, neurodegeneration, and central nervous system damage resulting from stroke, ischemia and trauma. The term "treatment" in the present context includes partial or total inhibition of dementias, including Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia and senile dementia.

Such compositions are useful in treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome and liver disease.

Such compositions are useful in treatment of pain, including but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer. For example, such compositions are useful for relief of pain, fever and inflammation in a

variety of conditions including rheumatic fever, influenza and other viral infections including common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, and trauma following surgical and dental procedures.

Such compositions are useful for, but not limited to, treating and preventing inflammation-related cardiovascular disorders in a subject. Such compositions are useful for treatment and prevention of vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

Such compositions are useful for, but not limited to, treatment of angiogenesis-related disorders in a subject, for example to inhibit tumor angiogenesis. Such compositions are useful for treatment of neoplasia, including metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, macular degeneration, retrolental fibroplasia and glaucoma, including neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemangiomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

Such compositions are useful for prevention or treatment of benign and malignant tumors/neoplasia including cancers, for example colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung

cancer, breast cancer and skin cancer, such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that affect epithelial cells throughout the body. Neoplasias for treatment of which compositions of the invention are contemplated to be particularly useful are gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreas cancer, ovary cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamous cell and basal cell cancers. Compositions of the invention can also be used to treat fibrosis that occurs with radiation therapy. Such compositions can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, such compositions can be used to prevent polyps from forming in patients at risk of FAP.

Such compositions inhibit prostanoid-induced smooth muscle contraction by preventing synthesis of contractile prostanoids and hence can be of use in treatment of dysmenorrhea, premature labor, asthma and eosinophil-related disorders. They also can be of use for decreasing bone loss particularly in postmenopausal women (*i.e.*, treatment of osteoporosis), and for treatment of glaucoma.

Preferred uses for compositions of the present invention are for treatment of rheumatoid arthritis and osteoarthritis, for pain management generally (particularly post-oral surgery pain, post-general surgery pain, post-orthopedic surgery pain, and acute flares of osteoarthritis), for treatment of Alzheimer's disease, and for colon cancer chemoprevention.

For treatment of rheumatoid arthritis or osteoarthritis, such compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, still more preferably about 175 mg to about 400 mg, for example about 200 mg. A daily dose of celecoxib of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 8 mg/kg body weight, more preferably about 2 to about 6.7 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 2.7 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to about four doses per day, preferably one or two doses per day.

For treatment of Alzheimer's disease or cancer, such compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 800 mg, more preferably about 150 mg to about 600 mg, and still more preferably about 175 mg to about 400 mg, for example about 400 mg. A daily dose of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 10.7 mg/kg body weight, more preferably about 2 to about 8 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 5.3 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to about four doses per day, preferably one or two doses per day.

For pain management generally and specifically for treatment and prevention of headache and migraine, such compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, and still more preferably about 175 mg to about 400 mg, for example about 200 mg. A daily dose of celecoxib of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 8 mg/kg body weight, more preferably about 2 to about 6.7 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 2.7 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to about four doses per day. Administration at a rate of one 50 mg dose unit four times a day, one 100 mg dose unit or two 50 mg dose units twice a day or one 200 mg dose unit, two 100 mg dose units or four 50 mg dose units once a day is preferred.

For selective cyclooxygenase-2 inhibitory drugs other than celecoxib, appropriate doses can be selected by reference to the patent literature cited hereinabove.

Besides being useful for human treatment, compositions of the invention are also useful for veterinary treatment of companion animals, exotic animals, farm animals, and the like, particularly mammals including rodents. More particularly, compositions of the invention are useful for veterinary treatment of cyclooxygenase-2 mediated disorders in horses, dogs and cats.

Method of treatment

The present invention also is directed to a therapeutic method of treating a condition or disorder where treatment with a cyclooxygenase-2 inhibitory drug is indicated, the method comprising oral administration of one or more pharmaceutical compositions of the present invention to a patient in need thereof. The dosage regimen to prevent, give relief from, or ameliorate the condition or disorder preferably corresponds to once-a-day or twice-a-day treatment, but can be modified in accordance with a variety of factors. These include the type, age, weight, sex, diet and medical condition of the patient and the nature and severity of the disorder. Thus, the dosage regimen actually employed can vary widely and can therefore deviate from the preferred dosage regimens set forth above.

Initial treatment of a patient suffering from a condition or disorder where treatment with a cyclooxygenase-2 inhibitory drug is indicated can begin with a dose regimen as indicated above. Treatment is generally continued as necessary over a period of several weeks to several months or years until the condition or disorder has been controlled or eliminated. Patients undergoing treatment with a composition of the invention can be routinely monitored by any of the methods well known in the art to determine the effectiveness of therapy. Continuous analysis of data from such monitoring permits modification of the treatment regimen during therapy so that optimally effective amounts of the drug are administered at any point in time, and so that the duration of treatment can be determined. In this way, the treatment regimen and dosing schedule can be rationally modified over the course of therapy so that the lowest amount of the drug exhibiting satisfactory effectiveness is administered, and so that administration is continued only for so long as is necessary to successfully treat the condition or disorder.

The present compositions can be used in combination therapies with opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among others. Preferred combination therapies comprise use of a composition of the invention with one or more compounds selected from aceclofenac, acemetacin,

e-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid (aspirin), *S*-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, α-bisabolol, bromfenac, *p*-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphene, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, *p*-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lornoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine

sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalmide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, piprofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide *o*-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen and zomepirac (see The Merck Index, 12th Edition (1996), Therapeutic Category and Biological Activity Index, lists therein headed "Analgesic", "Anti-inflammatory" and "Antipyretic").

Particularly preferred combination therapies comprise use of a composition of the invention, for example a celecoxib or valdecoxib composition of the invention, with an opioid compound, more particularly where the opioid compound is codeine, meperidine, morphine or a derivative thereof.

The compound to be administered in combination with celecoxib can be formulated separately from the celecoxib or co-formulated with the celecoxib in a composition of the invention. Where celecoxib is co-formulated with a second drug, for example an opioid drug, the second drug can be formulated in immediate-release, rapid-onset, sustained-release or dual-release form.

In an embodiment of the invention, particularly where the cyclooxygenase-2 mediated condition is headache or migraine, the present selective cyclooxygenase-2 inhibitory drug composition is administered in combination therapy with a vasomodulator, preferably a xanthine derivative having vasomodulatory effect, more

preferably an alkylxanthine compound.

Combination therapies wherein an alkylxanthine compound is co-administered with a selective cyclooxygenase-2 inhibitory drug composition as provided herein are embraced by the present embodiment of the invention whether or not the alkylxanthine is a vasomodulator and whether or not the therapeutic effectiveness of the combination is to any degree attributable to a vasomodulatory effect. The term "alkylxanthine" herein embraces xanthine derivatives having one or more C_{1-4} alkyl, preferably methyl, substituents, and pharmaceutically acceptable salts of such xanthine derivatives. Dimethylxanthines and trimethylxanthines, including caffeine, theobromine and theophylline, are especially preferred. Most preferably, the alkylxanthine compound is caffeine.

The total and relative dosage amounts of the selective cyclooxygenase-2 inhibitory drug and of the vasomodulator or alkylxanthine are selected to be therapeutically and/or prophylactically effective for relief of pain associated with the headache or migraine. Suitable dosage amounts will depend on the particular selective cyclooxygenase-2 inhibitory drug and the particular vasomodulator or alkylxanthine selected. For example, in a combination therapy with celecoxib and caffeine, typically the celecoxib will be administered in a daily dosage amount of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, and the caffeine in a daily dosage amount of about 1 mg to about 500 mg, preferably about 10 mg to about 400 mg, more preferably about 20 mg to about 300 mg.

The vasomodulator or alkylxanthine component of the combination therapy can be administered in any suitable dosage form by any suitable route, preferably orally. The vasomodulator or alkylxanthine can optionally be coformulated with the selective cyclooxygenase-2 inhibitory drug in a single oral dosage form. Thus an oral fast-melt composition of the invention optionally comprises both an aminosulfonyl-comprising selective cyclooxygenase-2 inhibitory drug and a vasomodulator or alkylxanthine such as caffeine, in total and relative amounts consistent with the dosage amounts set out hereinabove.

The phrase "in total and relative amounts effective to relieve pain", with respect to amounts of a selective cyclooxygenase-2 inhibitory drug and a vasomodulator or alkylxanthine in a composition of the present embodiment, means

that these amounts are such that (a) together these components are effective to relieve pain, and (b) each component is or would be capable of contribution to a pain-relieving effect if the other component is or were not present in so great an amount as to obviate such contribution.

Ingredients of compositions of the invention

A composition of the invention comprises as active ingredient a selective cyclooxygenase-2 inhibitory drug as hereinabove described, and various pharmaceutically acceptable excipients. Excipients that must be present are a saccharide having low moldability as herein defined, a saccharide having high moldability as herein defined, and, in a presently preferred embodiment, a wetting agent. Optionally, a composition of the invention can contain one or more additional pharmaceutically acceptable excipients including, but not limited to, water-soluble lubricants, water-insoluble lubricants, disintegrants, glidants, sweeteners, flavoring agents, colorants, *etc.* Such optional additional components should be physically and chemically compatible with the other ingredients of the composition and must not be deleterious to the recipient.

Active ingredient

In one embodiment, the selective cyclooxygenase-2 inhibitory drug is present in an amount of about 1% to about 75%, preferably about 5% to about 60%, and more preferably about 15% to about 60%, for example about 50%, by weight of the composition.

Particularly where the drug is one having a relatively high dosage requirement, such as celecoxib, a preferred composition comprises the drug in an amount of about 15% to about 75%, preferably about 30% to about 75%, and more preferably about 45% to about 75%, for example about 60%, by weight of the composition. We have been surprised that through the process of the present invention we have been able to formulate such an extremely hydrophobic drug as celecoxib at such high concentration in an oral fast-melt tablet.

Low moldability saccharide

Presently preferred low moldability saccharides include lactose and mannitol, particularly mannitol in its non-direct compression or powder form as described in

Handbook of Pharmaceutical Excipients, 3rd Ed. (2000), Pharmaceutical Press, pp. 324-328. One or more low moldability saccharides are present in compositions of the invention in a total amount of about 10% to about 90%, preferably about 15% to about 60%, and more preferably about 25% to about 50%, for example about 40%, by weight of the composition.

High moldability saccharide

Presently preferred high moldability saccharides include maltose, maltitol and sorbitol. Alternatively, certain oligosaccharides can be useful. The oligosaccharide used is not particularly limited so long as it shows rapid dissolution in the oral cavity and consists of two or more monosaccharide residues. Where an oligosaccharide is used, one consisting of 2 to 6 monosaccharide residues is preferable, and the type and combination of monosaccharide residues constituting the oligosaccharide are not limited. Particularly preferred high moldability saccharides are maltose and maltitol, more particularly maltose.

One or more high moldability saccharides are present in a total amount of about 1% to about 10%, preferably about 1% to about 7.5%, and more preferably about 1% to about 5%, by weight of the composition.

The weight ratio of high moldability saccharide to low moldability saccharide in a fast-melt tablet of the invention is important in maintaining a combination of acceptable tablet hardness and rapid intraoral disintegration. A suitable ratio is about 2 to about 20 parts by weight, preferably about 5 to about 10 parts by weight, and more preferably about 5 to about 7.5 parts by weight, of the high moldability saccharide per 100 parts by weight of the low moldability saccharide.

If the ratio of high to low moldability saccharide is less than about 2:100 by weight, tablets typically do not achieve their desired hardness, resulting in increased breakage during storage, transportation or handling. Alternatively, if the ratio of high to low moldability saccharide exceeds about 20:100 by weight, the tablets become too hard and desired rapid disintegration in the oral cavity is not achieved.

Wetting agents

In a preferred embodiment, compositions of the present invention comprise one or more pharmaceutically acceptable wetting agents. Surfactants, hydrophilic

polymers and certain clays can be useful as wetting agents to aid in wetting of a hydrophobic drug, such as celecoxib, by the granulation fluid during wet granulation. Where compositions of the present invention are made by the fluid bed granulation process, it is particularly advantageous that the composition contain a wetting agent. Importantly, however, where a relatively low dose cyclooxygenase-2 inhibitory drug such as valdecoxib is used and the concentration of the drug in the composition is therefore relatively low, a wetting agent may not be required, particularly if a glidant, for example silicon dioxide, is used.

Non-limiting examples of surfactants that can be used as wetting agents in compositions of the present invention include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and octoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (*e.g.*, Labrasol™ of Gattefossé), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example polyoxyethylene (20) cetostearyl ether, polyoxyethylene fatty acid esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (*e.g.*, Tween™ 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol laurate (*e.g.*, Lauroglycol™ of Gattefossé), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof. Sodium lauryl sulfate is a preferred wetting agent in compositions of the present invention.

One or more wetting agents, if desired, are present in compositions of the present invention in a total amount of about 0.05% to about 5%, preferably about 0.075% to about 2.5%, and more preferably about 0.25% to about 1%, for example about 0.5%, by weight of the composition.

Water-insoluble lubricants

Compositions of the present invention optionally comprise one or more

pharmaceutically acceptable water-insoluble lubricants as a carrier material. Suitable water-insoluble lubricants include, either individually or in combination, glyceryl behapate (*e.g.* Compritol™ 888), stearates (magnesium, calcium, and sodium), stearic acid, hydrogenated vegetable oils (*e.g.*, Sterotex™), colloidal silica, talc, waxes and mixtures thereof. Optionally a water-insoluble lubricant can be used in mixture with a wetting agent, as for example in calcium stearate/sodium lauryl sulfate mixtures (*e.g.*, Sterowet™).

Magnesium stearate, stearic acid and mixtures thereof are preferred water-insoluble lubricants.

One or more water-insoluble lubricants optionally are present in compositions of the present invention in a total amount of about 0.05% to about 5%, preferably about 0.75% to about 2.5%, and more preferably about 1% to about 2%, for example, about 1.5%, by weight of the composition.

Water-soluble lubricants

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable water-soluble lubricants. Water-soluble lubricants can help to improve tablet dissolution characteristics. Water-soluble lubricants that can be used in compositions of the present invention either individually or in combination include, for example, boric acid, sodium benzoate, sodium acetate, sodium fumarate, sodium chloride, DL-leucine, polyethylene glycols (*e.g.*, Carbowax™ 4000 and Carbowax™ 6000), and sodium oleate.

Disintegrants

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable disintegrants, particularly for tablet formulations. However, the oral fast-melt tablets provided herein typically disintegrate rapidly in the oral cavity and have no requirement for added disintegrant. Suitable disintegrants, if desired, include, either individually or in combination, starches, sodium starch glycolate, clays (such as Veegum™ HV), celluloses (such as purified cellulose, methylcellulose, sodium carboxymethylcellulose and carboxymethylcellulose), croscarmellose sodium, alginates, pregelatinized corn starches (such as National™ 1551 and National™ 1550), crospovidone, and gums (such as agar, guar, locust bean,

karaya, pectin and tragacanth gums). Disintegrants can be added at any suitable step during the preparation of the composition, particularly prior to granulation or during a blending step prior to tablet compression. Croscarmellose sodium and sodium starch glycolate are preferred disintegrants.

One or more disintegrants optionally are present in a total amount of about 0.5% to about 7.5%, preferably about 1% to about 5%, and more preferably about 1% to about 3.5%, by weight of the composition.

Optionally, an effervescent salt can be used as a disintegrant and to enhance organoleptic properties of a fast-melt tablet of the invention.

Glidants

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable glidants, for example to enhance flow of tableting material into tablet dies, to prevent sticking of tableting material to punches and dies, or to produce tablets having a sheen. Glidants may be added at any suitable step during preparation of the composition, particularly prior to granulation or during a blending step prior to tablet compression.

Without being bound by theory, it is believed that, in some situations, glidants, for example talc or silicon dioxide, act to reduce interfacial tension between drug particles, having the effect of inhibiting and/or reducing drug agglomeration, act to decrease electrostatic charges on the surface of drug powders, and act to reduce interparticular friction and surface rugosity of drug particles. See, for example, York (1975) J. Pharm. Sci., 64(7), 1216-1221. Use of a glidant such as silicon dioxide, therefore, can eliminate or reduce the need for a wetting agent in certain instances, for example, when formulating low dose selective cyclooxygenase-2 inhibitory drugs such as valdecoxib.

Silicon dioxide is a preferred glidant. Suitable silicon dioxide products for use in preparing compositions of the invention include fumed silica or colloidal silica (*e.g.*, Cab-O-Sil™ of Cabot Corp. and Aerosil™ of Degussa). Silicon dioxide, when present in compositions of the invention, is present in a total amount of about 0.05% to about 5%, preferably about 0.1% to about 2%, and more preferably about 0.25% to about 1%, for example, about 0.5%, by weight of the composition.

Sweetening agents

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable sweeteners. Non-limiting examples of sweeteners that can be used in compositions of the present invention include mannitol, propylene glycol, sodium saccharin, acesulfame K, neotame, aspartame, *etc.*

Flavoring agents

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable flavoring agents. Non-limiting examples of flavoring agents that can be used in compositions of the present invention include peppermint, spearmint, grape, cherry, strawberry, lemon, *etc.*

Tablet characteristics

Size and shape

In a preferred embodiment, compositions of the invention are in the form of discrete solid dosage units, most preferably tablets. Tablets of the invention can be made to any desired size, for example 8 mm, 10 mm, 12 mm, *etc.*; shape, for example round, oval, oblong, *etc.*; weight; and thickness. Optionally, solid dosage units of the invention may have etchings or monograms on one or both sides.

Disintegration

Preferred tablet compositions of the invention disintegrate within about 30 to about 300 seconds, more preferably within about 30 to about 200 seconds, and still more preferably within about 30 to about 150 seconds, in a standard *in vitro* disintegration assay (*e.g.*, conducted according to U.S. Pharmacopeia 24 (2000), Test No. 701).

Alternatively or additionally, preferred tablet compositions of the invention disintegrate within about 5 to about 60 seconds, more preferably within about 5 to about 40 seconds, and still more preferably within about 5 to about 30 seconds, for example about 25 seconds, after placement in the oral cavity of a subject.

Hardness

Solid dosage forms of the invention have a hardness that can depend on size and shape as well as on composition, among other characteristics. Tablet hardness can be measured by any method known in the art, for example by a tablet hardness

meter (*e.g.*, Schleuniger). Preferably, compositions of the invention have a hardness of about 1 to about 10 kp, and more preferably of about 1 to about 6 kp.

In a presently preferred embodiment, solid dosage forms of the invention have sufficient hardness for handling and, therefore, can be put into practical use in the same manner as the case of ordinary tablets. The term "sufficient hardness for handling" as used herein means a hardness which can withstand removal from at least a standard type of blister packaging, or such a hardness as will withstand other handling such as packaging, delivery, carrying and the like.

Tablets of the invention preferably have a minimum hardness so as to resist breakage of the tablet during removal from standard blister packaging by pushing the tablet through a cover sheet. A suitable hardness is about 1 kp or more for a tablet having a diameter of about 8 mm, about 1.5 kp or more for a tablet having a diameter of about 10 mm, and about 2 kp or more when the tablet has a diameter of about 12 mm.

In another presently preferred embodiment, tablets of the invention have sufficient hardness such that a plurality of such tablets can be packaged together, for example in a glass or plastic bottle, without individual packaging, yet do not exhibit substantial breakage or sticking and/or melding together during normal shipping and handling. Tablets intended for such packaging preferably have a hardness of about 3 kp or more.

Packaging

Compositions of the invention can be packaged in any suitable manner known in the art. For example, a multiplicity of fast-melt tablets can be packaged together, for example in a glass or plastic bottle or container. Alternatively, fast-melt tablets of the invention can be individually wrapped, for example in plastic or foil, or packaged in known forms of blister packaging. Blister packaging with improved force distribution properties such as is disclosed in U.S. Patent No. 5,954,204 to Grabowski, incorporated herein by reference, can be especially useful to package fast-melt tablets of the invention.

Administration of fast-melt tablets

Compositions of the present invention can be taken by a subject by any oral

administration means in accordance with the subject's choice or condition. For example, fast-melt tablets of the invention can be taken without water. Upon placement in the oral cavity and especially in the cheek or above the tongue, such a tablet is exposed to saliva and rapidly disintegrates and dissolves therein. The rate of disintegration and/or dissolution increases further when an intraoral pressure, for example a pressure between the palate and tongue or a licking or sucking pressure, is applied to the tablet.

Alternatively, a tablet of the present invention can be taken with the aid of water in an amount sufficient to wet the oral cavity and to assist in disintegration of the tablet. Also, a tablet of the invention can be swallowed together with a small amount of water after complete or partial disintegration in the oral cavity. Compositions of the invention can also be swallowed directly with water.

Method to make fast-melt tablets

The process described below is a non-limiting, illustrative method to make celecoxib fast-melt tablets. Importantly, specific settings and parameters of the production process can be readily optimized by one of skill in the art in order to produce tablets with particularly desired characteristics.

In this illustrative process, celecoxib and low moldability mannitol are de-lumped in a mill or grinder and blended to form a drug powder mixture. Next, this drug powder mixture is wet granulated, preferably by fluid bed granulation, with sodium lauryl sulfate and maltose solutions to form granules. If the granules are not dried during granulation, for example as is the case in fluid bed granulation, they are dried after granulation, for example in an oven. The resulting dried granules are then milled to form a milled granulate. The milled granulate is then optionally blended with flavor, sweetener and lubricants in a tumble blender to form a tablet blend. The resulting tablet blend is then compressed on a rotary tablet press to a target tablet weight and hardness. The resulting tablets are then subjected to treatment, for example air flow treatment, in a humidity-controlled chamber with the effect of increasing tablet hardness.

Wet granulation

Fluid bed granulation is the preferred method of wet granulation in processes

of the invention, although any known wet granulation method, for example high-shear granulation or pan granulation, can be used.

Illustratively, in fluid bed granulation, celecoxib, low moldability mannitol, and any other desired excipients are mixed together and sized in a mill or grinder. Next, the resulting drug powder mixture is granulated in a fluid bed by spraying a liquid solution of a high moldability saccharide and a wetting agent onto the mixture. The wet granules are then fluid bed dried.

After fluid bed granulation is complete, the resulting dried granules are then blended with any further desired excipients and then compressed into tablets.

Alternatively, in high-shear wet granulation, celecoxib, mannitol and any other desired excipients are blended under high shear in a granulator. Next, a liquid solution of high moldability saccharide and wetting agent are added to the resulting drug powder mixture under continuing high shear, thereby forming wet granules.

After high-shear granulation is complete, the resulting granules are then dried, for example, in an oven, microwave or fluid bed. The dried granules are then transferred to a blender for addition of any other desired excipients to form a tablet blend, which is then compressed.

Whether fluid bed or high-shear granulation is used, the celecoxib, low moldability mannitol and other excipients can, in an alternative process, be separately granulated and the resulting granules mixed together prior to compression.

Tablet compression

Compression is the process by which an appropriate volume of a tablet blend of granules produced as described above is compressed between an upper and lower punch to consolidate material into a single solid dosage form such as a tablet. In processes for manufacture of fast-melt tablets of the present invention, any suitable means for compression can be used including, for example, a single punch tablet machine or a high speed rotary tablet press. The tableting pressure is not limited, and an appropriate pressure can be selected depending on the desired hardness and dissolution properties of the resulting tablets. Where tablets are to undergo temperature and humidity treatment as described immediately below, the tablets are preferably compressed to an initial hardness (prior to temperature and humidity treatment) of about 0.75 to about 1.5 kp.

Temperature and humidity treatment

Optionally, tablets of the invention can undergo heat and humidity treatment after the tablet compression step. Such treatment can be performed in a humidity chamber, for example, to increase hardness of the tablets. Illustratively, during this treatment, tablets are first subjected to low temperature, high humidity air flow conditions, for example, about 25°C to about 32°C and about 80% relative humidity, for a period of about 45 to about 120 minutes. Tablets are then subjected to high temperature, low humidity conditions, for example about 35°C to about 50°C and 30% relative humidity for a period of about 45 to about 120 minutes. Without being bound by theory, it is believed that treatment of fast-melt tablets in a low temperature/high humidity chamber followed by treatment in a high temperature/low humidity chamber increases tablet hardness and reduces tablet friability without sacrificing desired fast-melt characteristics such as rapid disintegration and rapid dissolution.

EXAMPLES

The following examples illustrate aspects of the present invention but are not to be construed as limitations.

Example 1

Celecoxib fast-melt tablet formulations F1 to F7 were prepared having components as shown in Table 1, below. The formulations were prepared according to the following method.

1. Celecoxib and low moldability mannitol were de-lumped in a Co-mil producing a drug powder mixture.
2. The drug powder mixture was charged to a Glatt fluid bed processor and pre-heated. Inlet air was used to provide fluidization of the powder mixture. An aqueous sodium lauryl sulfate (1% by weight) solution and an aqueous maltose solution (5% to 6.5% by weight) were sprayed onto the fluidized powder bed resulting in wet granules. The wet granules were then fluid bed dried.
3. The resulting dried granules were subjected to a milling step through a Co-mil to form a milled granulate.

4. The milled granulate was blended with flavoring agent (spearmint flavor), sweetening agent (acesulfame K) and lubricants (magnesium stearate and stearic acid) in a tumble blender for approximately 5 to 10 minutes to form a blend.
5. The blend was then compressed on a rotary tablet press using a tooling size of 11.1 or 12.7 mm to form tablets having an initial hardness of about 0.5 to about 1.5 kp, and a target weight corresponding to a 200 mg dose of celecoxib.
6. The tablets were subjected to treatment in a chamber through which air at two specified sets of temperatures and relative humidity conditions was circulated. First, air at a temperature of 25°C and a relative humidity of 80% was circulated through the chamber for about 45 minutes. Second, air at a temperature of 50°C and a relative humidity of 30% was circulated through the chamber for about 45 minutes. Target final hardness was about 3 to about 4 kp.

Table 1. Composition (%) of fast-melt tablets F1 to F7

Formulation No.	F1	F2	F3	F4	F5	F6	F7
Tooling (mm)	11.1	11.1	12.7	12.7	11.1	11.1	11.1
Celecoxib	25.0	33.0	50.0	50.0	60.0	50.0	50.0
Mannitol [1]	66.75	58.75	40.25	41.75	31.75	41.75	39.25
Maltose	5.0	5.0	6.5	5.0	5.0	5.0	7.5
Magnesium stearate	0.75	0.75	0.75	0.75	0.75	0.75	1.0
Stearic acid	0.75	0.75	0.75	0.75	0.75	0.75	1.0
Sodium lauryl sulfate	1.0	1.0	1.0	1.0	1.0	3.0	1.0
Acesulfame K	0.5	0.5	0.5	0.5	0.5	4.0	0.5
Spearmint flavor	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Total (%)	100	100	100	100	100	100	100
Final Weight (mg)	400	400	400	400	400	400	400

[1] low moldability mannitol

Tablet hardness was determined by measuring the degree of force required to break the tablets. Tablet hardness data for formulations F1 to F7 are provided below in Table 2.

Disintegration profiles of tablets were evaluated in a standard *in vitro* disintegration assay (U.S. Pharmacopeia 24 (2000), Test No. 701) under the following

conditions. Tablets were placed into a basket-rack assembly containing 6 open-ended glass tubes held vertically upon a 10-mesh stainless steel wire screen. The baskets were then raised and lowered in an immersion fluid consisting of water at 37°C, at a frequency of 29 to 32 cycles per minute. Complete disintegration of tablets was recorded when no residue of the tablet remained on the screen of the test apparatus except that consisting of a soft mass having no palpably firm core. Tablet *in vitro* disintegration data for formulations F1 to F5 are provided below in Table 2, below.

In vivo disintegration profiles of tablets were evaluated in human subjects according to the following procedure. A subject placed a fast-melt tablet on his or her tongue and immediately started a chronometer. The subject gently moved the tablet against the upper part of the mouth with the tongue, creating gentle tumble action on the tablet without biting on it. The subject then stopped the chronometer immediately after the last noticeable granule disintegrated. Time to disintegration was then recorded.

In vivo disintegration data for formulations F1 to F7 are provided below in Table 2, below.

Table 2. Properties of celecoxib fast-melt tablet formulations F1 to F7

Formulation No.	F1	F2	F3	F4	F5	F6	F7
Mean *in vitro* disintegration time (sec.)	46	99.5	99.3	97.4	63.0	-	-
Mean *in vivo* disintegration time (sec.)	24.0	27.5	32.0	31.0	30.0	30.8	30.7
Mean hardness (kp)	3.6	3.6	2.4	4.0	2.7	3.5	3.2

Example 2

Celecoxib fast-melt tablet formulations F8 and F9 were prepared having components as shown in Table 3, below. The formulations were prepared according to the following method.

1. Celecoxib, silicon dioxide and low moldability mannitol were de-lumped in a Co-mil producing a drug powder mixture.
2. The drug powder mixture was charged to a Glatt fluid bed processor and pre-heated. Inlet air was used to provide fluidization of the powder bed, and an aqueous sodium lauryl sulfate solution (2.5% by weight) and an aqueous maltose solution (15% by weight) were sprayed onto the fluidized

powder bed resulting in wet granules. Importantly, no material stuck to the walls of the processor. The wet granules were then fluid bed dried.

3. The resulting dried granules were subjected to a milling step through a Co-mil to form a milled granulate.
4. The milled granulate was blended with flavoring agent (acesulfame K and peppermint flavor) and lubricants (magnesium stearate and stearic acid) in a tumble blender for about 5 minutes to form a blend.
5. The blend was then compressed in a Korsch press using a tooling of 11.9 mm, to form tablets having an initial target hardness of about 1.0 kp and a final tablet target weight of 400 mg.
6. The tablets were subjected to treatment in a chamber through which air at two specified sets of temperatures and relative humidity conditions was circulated. First, air at a temperature of 25°C and a relative humidity of 80% was circulated through the chamber for about 40 minutes. Second, air at a temperature of 50°C and a relative humidity of 30% was circulated through the chamber for about 60 minutes.

Table 3. Composition (mg) of celecoxib fast-melt formulations F8 and F9

Formulation No.	F8	F9
Tooling (mm)	11.9	12
Celecoxib	200	200
Mannitol [1]	165	167
Maltose	20.0	20.0
Magnesium stearate	3.0	3.0
Silicon dioxide	2.0	2.0
Stearic acid	3.0	3.0
Sodium lauryl sulfate	4.0	2.0
Acesulfame K	2.0	2.0
Spearmint flavor	1.0	1.0
Total	400	400

[1] low moldability mannitol

Table 4. Properties of celecoxib fast-melt tablet formulations F8 and F9

Formulation No.	F8	F9
Mean *in vitro* disintegration time (min.)	1.01	2.13
Mean *in vivo* disintegration time (sec.)	23	-
Final hardness (kp)	3.2 - 4.0	4.6 - 5.4

Example 3

Valdecoxib fast-melt tablet formulations F10 and F11 were prepared having components as shown in Table 4, below. The formulations were prepared according to the following method.

1. Valdecoxib, silicon dioxide and low moldability mannitol were de-lumped in a Co-mil producing a drug powder mixture.
2. The drug powder mixture was charged to a Glatt fluid bed processor and pre-heated. Inlet air was used to provide fluidization of the powder bed, and an aqueous maltose solution (15% by weight) was sprayed onto the fluidized powder bed resulting in wet granules. Importantly, no material stuck to the walls of the processor. The wet granules were then fluid bed dried.
3. The resulting dried granules were subjected to a milling step through a Co-mil to form a milled granulate.
4. The milled granulate was blended with flavoring agent (acesulfame K and peppermint or spearmint flavor) and lubricants (magnesium stearate and stearic acid) in a tumble blender for about 5 minutes to form a blend.
5. The blend was then compressed in a Korsch press using a tooling of 11.9 mm, to form tablets having an initial target hardness of about 1.0 kp and a final tablet target weight of 400 mg.
6. The tablets were subjected to treatment in a chamber through which air at two specified sets of temperatures and relative humidity conditions was circulated. First, air at a temperature of 25°C and a relative humidity of 80% was circulated through the chamber for about 40 minutes. Second, air at a temperature of 50°C and a relative humidity of 30% was circulated through the chamber for about 60 minutes.

Table 4. Composition (mg) of valdecoxib fast-melt formulations F10 and F11

Formulation No.	**F10**	**F11**
Tooling (mm)	11.9	11.9
Valdecoxib	40	40
Mannitol [1]	326	326
Maltose	20.0	20.0
Magnesium stearate	2.0	2.0
Silicon dioxide	2.0	2.0
Stearic acid	6.0	6.0
Acesulfame K	2.0	2.0
Spearmint flavor	2.0	-
Peppermint flavor	-	2.0
Total	400	400

[1] low moldability mannitol

EP 2 464 346 B1